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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/883,752	06/18/2001	John Charles Kath	PC 10760A	1737

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EXAMINER

BERCH, MARK L

ART UNIT

PAPER NUMBER

1624

DATE MAILED: 12/31/2002

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)
	09/883,752	KATH ET AL.
	Examiner Mark L. Berch	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 13 November 2002.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-21 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All
 - b) Some *
 - c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 - a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>3</u> .	6) <input type="checkbox"/> Other: _____

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 7-10, and 17-21 are rejected under 35 U.S.C. 102(e) as being anticipated by 6,284,764.

See examples 75, 76, 125 and 141. These correspond to the terminal heterocycle in R3 being pyridyl with t = 1 (methylene), R11 as Cl or methyl, m and t in R4 being zero, R4 as choice 1. R9 is piperidine substituted by OH, except in example 76 where there is an methyl substituent as well, and in example 75 where it is tetrahydropyran substituted by OH. The utility is the same.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 4, 5, 11, are rejected under 35 U.S.C. 103(a) as being unpatentable over 6,284,764.

See above rejection. Claim 4 corresponds to t = 0, whereas the prior art compounds have t = 1. However, the reference itself teaches such an equivalency. R3

can be R8, and R8 can be aryl (here, phenyl) substituted by R10 (see column 59, lines 34-35). For a choice for R10, see column 59, line 59, and note that if $t = 0$, this is the Heterocycle-(CR1R2) q -O- substituent seen here. Note that q can be 0-5 as seen at page 59, lines 62-63. Thus, the reference teaches this equivalence exactly. Similarly, the first two choices in claim 6 are thus obvious, as these raise exactly the same issue.

Claim 11, which has $k=1$ (rather than $k=0$ of the prior art compounds) presents a similar issue, except that it arises with R4, not R3. However, the reference at column 2, lines 62-63 teaches that $t = 0-5$, so that any number in that range is an obvious variation

Claim 5 has an additional issue, the 3-isomer, whereas the prior art compounds are the 2-pyridyl. It is well established that position isomers are *prima facie* structurally obvious even in the absence of a teaching to modify. The isomer is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing the position isomers. This circumstance has arisen many times. See: *Ex parte Englehardt*, 208 USPQ 343, 349; *In re Mehta*, 146 USPQ 284, 287; *In re Surrey*, 138 USPQ 67; *Ex Parte Ullerot*, 103 USPQ 185; *In re Norris*, 84 USPQ 459; *Ex Parte Naito*, 168 USPQ 437, 439; *Ex parte Allais*, 152 USPQ 66; *In re Wilder*, 166 USPQ 545, 548; *Ex parte Henkel*, 130 USPQ 474; *Ex parte Biel*, 124 USPQ 109; *In re Petrzilka*, 165 USPQ 327; *In re Crownse*, 150 USPQ 554; *In re Fouche*, 169 USPQ 431; *Ex parte Ruddy*, 121 USPQ 427; *In re Wiechert*, 152 USPQ 249, *In re Shetty*, 195 USPQ 753; *In re Jones*, 74 USPQ 152, 154.

For example, "Position isomerism has been used as a tool to obtain new and useful drugs" (*Englehardt*) and "Position isomerism is a fact of close structural

similarity" (Mehta, emphasis in the original). See also MPEP 2144.09, second paragraph.

Further, the reference itself teaches such an equivalency. R3 can be R8, and R8 can be aryl (here, phenyl) substituted by R10 (see column 59, lines 34-35). For a choice for R10, see column 59, line 59, and note that if t = 0, this is the Heterocycle-(CR1R2)q-O- substituent seen here. The heterocycle can thus be bound in any position (see also column 11, lines 53-55), not just the 2-position of the examples.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 7-11, and 17-21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,284,764. Although the conflicting claims are not identical, they are not patentably distinct from each other because of reasons given above. The same issues arise.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other forms, does not reasonably provide enablement for solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are drawn to solvates. But the hundreds of examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 “The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist.” The same circumstance appears to be true here: there is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

Claims 1-15 and 17-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for most choices, does not reasonably provide enablement for unsaturation in the $-(CR^1R^2)_n$ moiety. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

A double bond would make the carbons 5 coordinate, and a triple bond would make the carbons with 6 bonds. These are impossible.

Claims 17-19 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Certain variables, especially R4, R5, R3 and R11 are defined very broadly, two of which can appear multiple times. The genus covers trillions of compounds.

(b) Scope of the diseases covered. The coverage of claim 18 --- cancer --- is immense. There are hundreds of types of cancers and tumors. They can occur in pretty much every part of the body.

Claim 17 is even broader, as it covers any abnormal tissue that grows by cellular proliferation more rapidly than normal, or continues to grow after the stimulus that initiated the new growth has ceased, or shows lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such a term, covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, and polyps. In addition, it embraces various non-cancerous proliferative disorders such as psoriasis, restinosis, vascular smooth muscle proliferation associated with atherosclerosis, glomerular nephritis, clonal proliferative disorders including the various Myelodysplastic Syndromes such as Refractory anemias, certain types of abnormal wound healings, assorted types of abnormal angiogenesis, pulmonary fibrosis, macular degeneration, myeloproliferative disorders such as primary polycythemia and myleofibrosis, and rheumatoid arthritis.

Claim 17 is narrower than all cancers, but it still covers an immense range. This is not only because so many diverse cancers are named, but because some of these listed are themselves categories, sometimes large and diverse. For example, CNS cancers cover a very diverse range of cancers in many categories and subcategories. There are an immense range of neuroepithelial tumors. These include astrocytic tumors (e.g. astrocytomas and glioblastoma multiform) oligodendroglial tumors, Ependymal cell tumors (e.g. myxopapillary ependymoma), mixed gliomas (e.g. mixed oligoastrocytoma and ependymo-astrocytomas) tumors of the choroid plexus, neuronal and mixed neuronal-glial tumors (e.g. gangliocytoma, gangliogliomas, central neurocytoma, dysembryoplastic neuroepithelial tumor, esthesioneuroblastoma), pineal parenchyma tumors (e.g. pineocytoma, pineoblastoma), embryonal tumors (e.g.

medulloepithelioma, neuroblastoma, retinoblastoma, ependymoblastoma) and others such as polar spongioblastoma and Gliomatosis cerebri. A second Division is tumors of the meninges. This includes tumors of the meningotheelial cells, including Meningiomas (including fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous, microcystic, secretory, clear cell, chordoid, lymphoplasmacyte-rich, and metaplastic subtypes) and others such as papillary anaplastic meningioma. The category also includes non-meningotheelial tumors of the meninges. Examples are benign mesenchymal tumors (e.g. osteocartilaginous tumors), malignant mesenchymal tumors (e.g. chondrosarcoma, hemangiopericytoma, rhabdomyosarcoma and meningeal sarcomatosis) primary melanocytic Lesions (e.g. diffuse melanosis, melanocytoma), hemopoietic neoplasms (e.g. plasmactoma). A third Division are the tumors of Cranial and Spinal Nerves. This includes schwannomas, neurofibroma, and malignant peripheral nerve sheath tumor (MPNST). A fourth division are Germ Cell Tumors, including germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma. A fifth division are the tumors of the Sellar Region, viz. pituitary adenoma, pituitary carcinoma and craniopharyngioma. Yet another division are local extensions from regional tumors, including paraganglioma, chondroma, chordoma, and chondrosarcoma. And there are many, many others. There is also mentioned lung cancer, the main types of which are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. Included in claim 19 also are bone tumors, which would cover Osteosarcomas (osteoblastic, chondroblastic, fibroblastic, telangiectatic, and others), Hemangiosarcoma, Periosteal chondrosarcoma, Periosteal fibrosarcoma, Maxillary

fibrosarcoma, Parosteal osteosarcoma, Periosteal osteosarcoma, Malignant mesenchymoma, Liposarcoma, synovial sarcoma, Osteochondroma, Hemangioma, Myxoma of the jaw, Ossifying fibroma, Osteoma, Giant cell tumor of bone, multiple myeloma, solitary myeloma, reticulum cell sarcoma, malignant fibrous histiocytoma, desmoblastic fibroma of the bone, periosteal fibroma, lipoma, Hemangioendothelial sarcoma, Ewing's sarcoma, chondroblastoma, and Multilobular tumor of bone. There is also listed leukemia; there are dozens of leukemias. There are B-Cell Neoplasms such as B-cell prolymphocytic leukemia and Hairy cell leukemia. There are T-Cell Neoplasms such as T-cell prolymphocytic leukemia, aggressive NK cell leukemia, and T-cell granular lymphocytic leukemia. There are different kinds of acute myeloid leukemias, acute promyelocytic leukemias, acute myelomonocytic leukemia, chronic myelomonocytic leukemia, acute monocytic leukemias, and erythroleukemias. There is also acute megakaryoblastic leukemia, acute promyelocytic leukemia, Multiple Myeloma, lymphoblastic leukemia, hypocellular acute myeloid leukemia, Ph-/BCR-myeloid leukemia, acute basophilic leukemia, acute myelofibrosis, chronic granulocytic leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia and many others. In addition, the claim names assorted melanomas, carcinomas, adenomas, etc.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information given on page 27 is without regard to what particular disorder it is for.

(4) State of the Prior Art: The prior art knows that there never has been a compound capable of treating cancer generally. There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. As an example, Leukemias can arise from many different sources. These includes viruses such as EBV, which causes Burkitt's lymphoma, and HTLV-1, linked to certain T cell leukemias. Others are linked to genetic disorders, such as Fanconi's anemia, which is a familial disorder, and Down's Syndrome. Other leukemias are caused by exposure to carcinogens such as benzene, and some are actually caused by treatment with other neoplastic agents. Still other leukemias arise from ionizing radiation, and many are idiopathic. Leukemias also differ greatly in the morphology, degree of differentiation, body location (e.g. bone marrow, lymphoid organs, etc.) Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities.

(5) Working Examples: There are none. Hundreds of compounds have been prepared, but there is no evidence of any testing.

(6) Skill of those in the art: It is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available. The majority of common cancers do not respond to chemotherapy.

(7) The quantity of experimentation needed: Given the fact that historically the development of new cancer drugs has been difficult and time consuming, and especially in view of factors 1 and 4, the quantity of experimentation needed is expected to be great.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: The filing date for the provisional is listed as 6/20/2002, but PTO records state that the correct date is 6/22/2002.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.



Mark L. Berch
Primary Examiner
Art Unit 1624

December 30, 2002